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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/423,517	02/10/00	DA SILVA FREIRE M	3673-2

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NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON VA 22201-4714

EXAMINER	
ZEMAN,R	
ART UNIT	PAPER NUMBER
1645	11

DATE MAILED: 05/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/423,517	Da Silva Freire et al.
Examiner	**Art Unit**
Robert A. Zeman	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 10, 2000* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above, claim(s) *16-29* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-15 and 30-41* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-41* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group I in Paper No. 10 is acknowledged. The traversal is on the ground(s) that a search of all the claimed subject matter would not be an undue burden on the Examiner. This is not found persuasive because a search of both Groups would require non-overlapping searches since they do not encompass the same subject matter..

The requirement is still deemed proper and is therefore made FINAL.

Claims 16-29 have been withdrawn from consideration. Claims 1-15 and 30-41 are pending and currently under examination.

Claim Objections

Claims 9 and 36 are objected to because of the following informalities: The term "stabilizer" should be preceded by the article "a".. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 30-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims are confusing and filled with multiple errors some of which are described below. It is suggested that the claims, as a whole, be rewritten in accordance with U.S practice.

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "acceptable as a substrate for vaccine production". It is unclear what is meant by this phrase. What is an acceptable substrate? What criteria is used to make such an evaluation? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "suitable medium". Suitable for what? It is unclear what limitation Applicant is claiming. As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "**the** cell culture". To which cell culture is Applicant referring? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "appropriate period of time". Appropriate for what?

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "once or more times".

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "harvesting of culture supernatant containing virus with or without addition of stabilizer". It is unclear what is meant by this phrase. Is the stabilizer optionally part of the virus containing culture supernatant or optionally added during harvesting of said supernatant? As written, it is impossible to determine the metes and bounds of the claimed invention. Additionally, said claim is grammatically incorrect as the term "stabilizer" should be preceded by the article "a".

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "optionally, removing cell debris and whole cells from **the** harvested virus" This phase is confusing. How can a whole cell be removed from a virus? Additionally, which specific virus particle is Applicant referring to? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 1 and 30 are rendered vague and indefinite by their use of the phrase "optionally, virus inactivation" It is unclear what is meant by this phrase. What is an acceptable substrate? How is said inactivation to be done? When? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 2 and 31 are rendered vague and indefinite by reciting improper Markush language. Additionally, the phrase "such as" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 2 and 31 are rendered vague and indefinite by the use of the phrase "submitted to viral infection". It is unclear what is meant by said phrase. Does Applicant mean "subjected to

viral infection"? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 3 and 32 are rendered vague and indefinite by the use of the phrase "any further passaged". It is unclear what may be "further passaged".

Claims 7, 8 and 35 are rendered vague and indefinite by the phrase "culture is incubated at steps x, y and z from 12 to 72 (or 144) hours". It is unclear whether the time is a cumulative time or is applied to each step individually. As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 10 and 37 are rendered vague and indefinite by the use of the phrase "acceptable as a component in parenteral products". It is unclear what is meant by this phrase. What "parenteral products"? What makes a component acceptable? What criteria is used to make such an evaluation? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 11 and 38 are rendered vague and indefinite by the use of the term "wild". It is unclear what is meant by said term. Is Applicant referring to wild-type strains? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claims 15 and 41 are rendered vague and indefinite by the use of the phrase "YF17D strain **and** substrains thereof". It is unclear what limitation is being claimed. Are the cells infected with multiple strains/substrains of Yellow Fever virus simultaneously or is a single strain/substrain used? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7, 9-10, 12-14, 30-32 and 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Barrett et al. (Journal of General Virology, Vol. 71 1990, pages 2301-2306).

The instant claims are drawn to methods of virus propagation comprising incubating permissive cells with a virus of a given period of time, removing said inoculum, replenishing growth medium, incubating cells for a given period of time after which the growth medium is harvested (and subsequently replaced). The claims recite the following limitations: the virus being propagated is a wild-type Yellow fever virus or an attenuated Yellow fever virus; cells being infected produce interferon in response to viral infection; the incubation and culture time is between 12 and 144 hours (combined) and a stabilizer is used in the growth medium (FBS). Barrett et al. disclose a method of attenuating wild-type Yellow fever virus by passage in HeLa cells. Said reference discloses a method for infecting monolayers of HeLa cells with wild-type/attenuated Yellow fever virus wherein said cells were incubated with said virus, washed after a incubation period and incubated at 37 degrees Celsius to allow for virus production. After 4

days the medium was removed/replaced and clarified. The resulting virus was then used to infect subsequent HeLa cell cultures.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 and 30-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. (Journal of General Virology, Vol. 71 1990, pages 2301-2306).

The instant claims are drawn to methods of virus propagation comprising incubating permissive cells with a virus of a given period of time, removing said inoculum, replenishing growth medium, incubating cells for a given period of time after which the growth medium is

harvested (and subsequently replaced). The instant claims recite the following limitations: the virus being propagated is a wild-type Yellow fever virus or an attenuated Yellow fever virus (specifically YF-17D); cells being infected produce interferon in response to viral infection; said cells are seeded at a density of 1 x 10^4-1 x 10^5 cells/cm^2; the incubation and culture time is between 12 and 72 hours (combined); and a stabilizer is used in the growth medium. Barrett et al. disclose a method of attenuating wild-type Yellow fever virus by passage in HeLa cells. Said reference discloses a method for infecting subconfluent monolayers of HeLa cells with wild-type/attenuated Yellow fever virus wherein said cells were incubated with said virus, washed after a incubation period and incubated at 37 degrees Celsius to allow for virus production. After 4 days the medium was removed/replaced and clarified. The resulting virus was then used to infect subsequent HeLa cell cultures. Bartlett et al. differs from the instant invention in that it does not specifically recite the use of seeding the permissive cells at 1 x 10^4-1 x 10^5 cells/cm^2 or harvesting the infected cultures within 72 hours. These differences, however, constitute an optimization of the method disclosed by Bartlett et al and would have been obvious to one of skill in the art. Additionally, the use of the YF-17D virus in lieu of the YF-Asibi virus disclosed by Bartlett et al. would be equally obvious to one of skill in the art since YF-17D is the standard strain used in vaccine production.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032 or the examiner's supervisor, Lynette Smith, can be reached at (703)308-3909.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman

May 29, 2001